

REMARKS

Claims 1-3, 5-9 and 18-30 are pending in the instant specification. Applicants have amended claims 1, 2, 5 and 8. Support for the amendment to claim 1 can be found, for example, from page 3, line 12 to page 4, line 5 of the instant specification. Support for the amendment to claim 5 can be found, for example, from page 6, line 14 to page 7, line 5 of the instant specification. Applicants have added claims 18-30. Support for claims 18-24 can be found, for example, in claims 1-3 and 5-9 as previously presented and on page 9, line 21 of the instant specification. Support for claims 25-30 can be found, for example, in claims 1-3 and 5-9 as previously presented. Applicants have canceled claims 11 and 12 and reserve the right to pursue these claims in a continuation application. No new matter is added.

Claim Objections

The Examiner has objected to claim 8 for reciting “employed are in step”. Applicants have amended claim 8 to delete “are” from this phrase. Applicants submit that the objection is overcome.

Claim Rejections

35 U.S.C. §112, First Paragraph

The Examiner has rejected claim 2, on pages 4-5 of the Office Action, under 35 U.S.C. §112, first paragraph for lack of written description (new matter). The Examiner asserted that the addition of “NAD⁺” to the phrase “alteration in NADH ratio” was new matter. Applicants have amended claim 2 to delete the phrase, “alteration in NAD⁺/NADH ratio” rendering this rejection moot as it regards this claim.

35 U.S.C. §102

The Examiner has rejected claims 1-2, 5-6 and 9 on pages 6-7 of the Office Action, under 35 U.S.C. § 102(e) for being anticipated by Poellinger *et al.* U.S. Publication No. 2002-0048794 (“Poellinger”). The Examiner alleged that Poellinger teaches establishing a protein interaction

map according to the limitations of claims 1-2, 5-6 and 9. Applicants have amended claims 1 and 5 and traverse the rejection for the reasons explained below.

Poellinger does not teach the establishment of a protein-protein interaction map wherein the changed protein interaction is for the comparison of or involvement in one or more pathophysiological processes or one or more physiological processes. The Examiner alleged, on page 7 of the Office Action, that because the VHL gene is associated with von Hippel-Lindau disease, that the teachings of Poellinger show a protein-protein interaction map involving pathophysiological processes or physiological processes. However, Applicants submit that Poellinger teaches that the HIF-1/VHL interaction did not change under normoxic or hypoxic conditions.¹ The only protein-protein interaction that changed between normoxic or hypoxic conditions was an interaction between HIF-1 and Arnt, shown in Figure 20 of Poellinger. Nevertheless, this interaction does not involve a pathophysiological process or a physiological process.

The modulation of HIF-1/Arnt binding is due to nuclear localization of HIF-1 under hypoxic conditions.² As shown in Figure 25 of Poellinger, under normoxic conditions, despite VHL binding, HIF-1 α is polyubiquitinated and degraded. Under hypoxic conditions, HIF-1 α undergoes nuclear translocation rendering it available for Arnt binding. Poellinger does not teach any circumstances under which HIF-1 α would be available for binding with Arnt under normoxic conditions. Thus, any differential HIF-1/Arnt interaction under normoxic as compared to hypoxic conditions cannot involve a pathophysiological process or a physiological process.

Applicants have amended claims 1 and 5 from which claims 2, 6 and 9 depend, to state that the changed protein interaction forming the protein-protein interaction map must be involved in one or more pathophysiological processes or one or more physiological processes. Poellinger does not teach this limitation of claims 1, 2, 5, 6 and 9. Thus, Poellinger cannot anticipate claims 1, 2, 5, 6 and 9 as amended, herein. Thus, Applicants request that this rejection be withdrawn.

Further, Poellinger does not anticipate new claims 18-24. Claims 18-24 stipulate that the screening must be performed using a yeast two hybrid system. Poellinger does not teach a yeast

¹ Poellinger at paragraph 139 and Figures 19 and 20.

² *Id.* at paragraph 152.

two hybrid system used for screening of protein-protein interactions with and without a redox state perturbation. The only mention of a yeast two hybrid system in Poellinger is in the context of testing whether substances interact with a peptide at paragraph 34. Thus, Applicants submit that Poellinger cannot anticipate claims 18-24.

Further, Poellinger does not anticipate new claims 25 and 26. Poellinger does not teach the formation of a protein interaction map with the use of simulated redox state perturbation generated by a process selected from the group consisting of: variation of concentration of redox state modifier molecules from physiological state, variation of glucose concentration from physiological state, presence of metal ions and decreased oxygen tension from that in room air wherein a plurality of determinations are made in step (b) with different oxygen tensions being employed in each determination as recited in claim 25. Poellinger also does not teach the correlation of protein-protein interaction(s) with oxygen tension when a plurality of determinations are made in the presence of decreased oxygen tension with different oxygen tensions being employed in each determination as recited in claim 26. Thus, Applicants submit that Poellinger cannot anticipate claims 25 and 26.

The Examiner has explained in the previous Office Action that claims corresponding to new claims 27-30 are allowable. This is discussed in greater detail below. Therefore, Poellinger cannot anticipate claims 27-30.

Applicants submit that Poellinger does not teach all of the limitations of claims 1, 5, 6, 9 and 18-30 and thus cannot anticipate these claims. Applicants request that this rejection be withdrawn.

The Examiner has rejected claims 1-3 on pages 7-8 of the Office Action, under 35 U.S.C. § 102(a) for being anticipated by Dedio *et al.* The FASEB Journal 15(1):79-89 (2001) ("Dedio"). The Examiner alleged that Dedio teaches all of the limitations of claims 1-3. Specifically, the Examiner indicated that Figure 2 and page 83 of Dedio show that there is an interaction between eNOS and NOSIP but not eNOS and GFP in the presence and absence of A23187, thus implying that A23187 is a redox state modifier. Applicants respectfully disagree.

Dedio does not teach the establishment of a protein-protein interaction map in the absence and presence of a redox state perturbation. A23187 is a calcium ionophore, not a redox state modifier.³ It was added to see if the NOSIP-eNOS interaction was due to calcium induced regulation.⁴ Further, GFP was not immunoprecipitated both in the presence of absence of A23187.⁵ Thus, even if A23187 was a redox state modifier (Applicants argue that A23187 is not a redox state modifier) the screening of the at least one protein would not be performed with a plurality of proteins in the presence of a simulated redox state perturbation as required by claim 1. Dedio does not teach all of the limitations of claims 1-3 and thus cannot anticipate them. Applicants request that this rejection be withdrawn.

Allowable Subject Matter

The Examiner stated that claim 7 was objected to for being dependent upon a rejected claim, but would be allowable if rewritten in independent form. Applicants have done this by adding new claims 27-30. Thus, Applicants submit that claims 27-30 are allowable.

³ See Dedio in the Abstract.

⁴ *Id.* at page 83, column 1, end of first full paragraph.

⁵ *Id.* at Figure 2B.

CONCLUSION

A favorable action on the merits is respectfully requested. If further discussion of this case is deemed helpful, the Examiner is encouraged to contact the undersigned at the telephone number provided below, and is assured of full cooperation in progressing the instant claims to allowance.

Respectfully submitted,



Ivor R. Elrifi, Reg. No. 39,529
Sean M. Coughlin, Reg. No. 48,593
Attorney/Agent for Applicants
c/o Mintz, Levin
Telephone: (617) 542 6000
Fax: (617) 542 2241
Customer No. 30623

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